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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 38/05, C07D 211/14, 265/28</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/56765</p> <p>(43) International Publication Date: 11 November 1999 (11.11.99)</p>		
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/US99/09463</p> <p>(22) International Filing Date: 30 April 1999 (30.04.99)</p> <p>(30) Priority Data: 60/084,320 5 May 1998 (05.05.98) US</p> <p>(71) Applicants (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). BASF AKTIENGESELLSCHAFT [DE/DE]; ZHV/W-A30, Carl-Bosch-Strasse 38, D-67056 Ludwigshafen (DE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): CAPRATHE, Bradley, William [-/US]; 31480 Myma, Livonia, MI 48154 (US). GILMORE, John, Lodge [-/US]; 27 Ridgewood Circle, Wilmington, DE 19809 (US). HARTER, William, Glen [-/US]; 3750 Shagbark, Chelsea, MI 48118 (US). HAYS, Sheryl, Jeanne [-/FR]; 45, rue Notre Dame des Champs, F-75006 Paris (FR). KNAPP, Kristen, Michele [-/US]; 1231 Elbridge, Ypsilanti, MI 48197 (US). KOSTLAN, Catherine, Rose [-/US]; 9876 Moon Road, Saline, MI 48176 (US). LUNNEY, Elizabeth, Ann [-/US]; 619 Ridgewood Court, Ann Arbor, MI 48103 (US). PARA, Kimberly, Suzanne [-/US]; 2735 Dexter Avenue, Ann Arbor, MI 48103 (US).</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>GALATSIS, Paul [-/US]; 2400 Rockport Court, Ann Arbor, MI 48103 (US). THOMAS, Anthony, Jerome [-/US]; 2909 Brockman Boulevard, Ann Arbor, MI 48104 (US).</p> <p>(74) Agent: GRAY, Arthur, D.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).</p> <p>(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p> </td> </tr> </table>			<p>(21) International Application Number: PCT/US99/09463</p> <p>(22) International Filing Date: 30 April 1999 (30.04.99)</p> <p>(30) Priority Data: 60/084,320 5 May 1998 (05.05.98) US</p> <p>(71) Applicants (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). BASF AKTIENGESELLSCHAFT [DE/DE]; ZHV/W-A30, Carl-Bosch-Strasse 38, D-67056 Ludwigshafen (DE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): CAPRATHE, Bradley, William [-/US]; 31480 Myma, Livonia, MI 48154 (US). GILMORE, John, Lodge [-/US]; 27 Ridgewood Circle, Wilmington, DE 19809 (US). HARTER, William, Glen [-/US]; 3750 Shagbark, Chelsea, MI 48118 (US). HAYS, Sheryl, Jeanne [-/FR]; 45, rue Notre Dame des Champs, F-75006 Paris (FR). KNAPP, Kristen, Michele [-/US]; 1231 Elbridge, Ypsilanti, MI 48197 (US). KOSTLAN, Catherine, Rose [-/US]; 9876 Moon Road, Saline, MI 48176 (US). LUNNEY, Elizabeth, Ann [-/US]; 619 Ridgewood Court, Ann Arbor, MI 48103 (US). PARA, Kimberly, Suzanne [-/US]; 2735 Dexter Avenue, Ann Arbor, MI 48103 (US).</p>	<p>GALATSIS, Paul [-/US]; 2400 Rockport Court, Ann Arbor, MI 48103 (US). THOMAS, Anthony, Jerome [-/US]; 2909 Brockman Boulevard, Ann Arbor, MI 48104 (US).</p> <p>(74) Agent: GRAY, Arthur, D.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).</p> <p>(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
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<p>(54) Title: SUCCINAMIDE INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME</p> <div style="text-align: center; margin: 20px 0;"> <p style="margin-left: 150px;">(I)</p> </div> <p>(57) Abstract</p> <p>The present invention provides compounds of Formula (I), pharmaceutical compositions comprising a compound of Formula (I), and methods of treatment of stroke; inflammatory diseases such as rheumatoid arthritis or inflammatory bowel disease; septic shock; reperfusion injury; Alzheimer's disease; shigellosis; and multiple sclerosis.</p>				

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/09463

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/05; C07D 211/14, 265/28

US CL :514/19; 544/121,162,231,360

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/19; 544/121,162,231,360

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DANG et al. Preparation of an Autolysis-Resistant Interleukin-1B Converting Enzyme Mutant. Biochemistry. 1996, Vol. 35, No. 47 pages 14910-14916.	1-19
A	US 5,559,232 A (ACKERMAN et al.) 24 SEPTEMBER 1996, see entire patent.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 JULY 1999

Date of mailing of the international search report

17 AUG 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

BENNETT CELSA

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/09463

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-19
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group 1, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is hydrogen; and 1st method of use in treating stroke.

Group 2, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is an (un)substituted aryl group substituted aminosulfoxide (two structures on page 94, lines 15 and 20); and 1st method of use in treating stroke.

Group 3, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is dimethyl cyclohexyl(one) substituted aminosulfoxide (3 structures on pages 94-95); and 1st method of use in treating stroke.

Group 4, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is a dimethylcyclopentanone substituted aminosulfoxide (second structure on page 95); and 1st method of use in treating stroke.

Group 5, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is (un)substituted aryl group substituted alkylsulfinyl (fourth and fifth structures on page 95); and 1st method of use in treating stroke.

Group 6, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is the fifth structure on page 95; and 1st method of use in treating stroke.

Group 7, claim(s) 1-19 (IN PART), drawn to FORMULA I compounds in which Y is an Asp derivative, X is sixth structure on page 95; and 1st method of use in treating stroke.

Group 8, claim(s) 1-5 (IN PART) and 8-19 (IN PART), drawn to FORMULA I compound in which Y is a succinimyl derivative (second Y structure on page 93) and 1st method of use in treating stroke.

Group 9, claim(s) 1-5 (IN PART) and 8-19 (IN PART), drawn to FORMULA I compound in which Y is a cyano derivative (third Y structure on page 93); and 1st method of use in treating stroke.

Groups 10-18 claim (s) 20-23, drawn to second method of using a compound of one of Groups 1 to 9 above to treat inflammation.

Groups 19-27 claim(s) 24-25, drawn to third method of using a compound of one of Groups 1-9 above to treat septic shock.

Groups 28-36, claim(s) 26-27, drawn to fourth method of using a compound of one of Groups 1-9 above to treat reperfusion injury.

Groups 37-45, claim(s) 28-29, drawn to fifth method of using a compound of one of Groups 1-9 above to treat Alzheimers.

Groups 46-54, claim(s) 30-31, drawn to sixth method of using a compound of one of Groups 1-9 above to treat shigelolosis.

Group 55-63, claim(s) 32-33, drawn to seventh method of using a compound of one of Groups 1-9 above to treat multiple sclerosis.

Group 64-72, claim(s) 34-35, drawn to eight method of using a compound of one of Groups 1-9 above to inhibit ICE.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09463

The inventions listed as Groups 1-9 do not relate to a single inventive concept under PCT Rule 13.1 and 13.2 because these compounds lack the same or corresponding special technical features for the following reasons: The Group 1-9 compounds lack a significant structural element (e.g. core) which is shared by all of the alternatives which elicits a common activity nor do the different alternatives represent a recognized class of chemical compounds so as to constitute a proper Markush group. Further, the lack of any significant core structure shared by Groups 1-9 precludes the ability to conduct a meaningful search. Groups 10-72 represent further methods of use which represent different and diverse diseases or conditions which require different etiologies and fail to share a special technical feature. It is also noted that pursuant to Rule 13, a compound is only entitled to be linked to a single method of use, with additional methods constituting additional groups.

Upon the non-payment of fees to additional groups, the search will be limited to only the Group 1 invention.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D 28 APR 2000

WIPO

PCT

(PCT Article 36 and Rule 70)

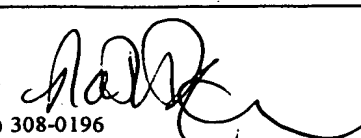
Applicant's or agent's file reference PD-5645-01-T	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/09463	International filing date (day/month/year) 30 APRIL 1999	Priority date (day/month/year) 05 MAY 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 38/05; C07D 211/14, 265/28 and US Cl.: 514/19; 544/121, 162, 231, 360		
Applicant WARNER-LAMBERT COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17 NOVEMBER 1999	Date of completion of this report 29 MARCH 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BENNETT CELSA  Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09463

I. Basis of the report

1. With regard to the **elements** of the international application:*☒ the international application as originally filed☒ the description:

pages 1-92, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the claims:

pages 93-110, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the drawings:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/09463

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 20-35

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _ are so unclear that no meaningful opinion could be formed (*specify*).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 20-35.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09463

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)

Claims	<u>1-19</u>	YES
Claims	<u>NONE</u>	NO

Inventive Step (IS)

Claims	<u>1-19</u>	YES
Claims	<u>NONE</u>	NO

Industrial Applicability (IA)

Claims	<u>1-19</u>	YES
Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-19 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest formula I compounds in which Y is an asp derivative and X is hydrogen and the use thereof in treating stroke as presently claimed.

Claims 1-19 meet the criteria set out in PCT Article 33(4), for industrial applicability.

----- NEW CITATIONS -----
NONE